

LETTER TO THE EDITOR

Translating neuroscience research to oral medicine: oxytocin and human behavior

Dear Editor,

The neuropeptide oxytocin is known in mammalian species to facilitate uterine contractions during birth as well as to play a role in the release of milk; however, research has now demonstrated that oxytocin modulates a variety of behaviors in addition to its functions associated with birth and lactation. It is basic to prosocial behavior, is critical to social attachment and affiliation, bonds mother and child, reduces stress-related behaviors and anxiety, increases pain tolerance, increases trust, increases emotional empathy, promotes cooperation, is associated with 'falling in love', and accompanies sexual desire and orgasm. One prominent researcher in the field has designated oxytocin as the 'moral molecule' based on its role in emotional empathy, trust, generosity, and cooperative behavior (Zak, 2012). Oxytocin has been called the 'great facilitator of life' (Lee *et al.*, 2009).

Given the broad range of effects, oxytocin has on social behavior the question emerges as to what role oxytocin may play in behaviors associated with oral health care. While there has been an extraordinary proliferation of research relating oxytocin to humans, no studies have been identified relating oxytocin to behavioral issues associated with the seeking or provision of oral health care. A review of the neurobiology of the oxytocin system and its effect on human behavior, including psychosocial dysfunctions, suggests opportunities for research in oral medicine.

Neurobiology of oxytocin

Oxytocin is synthesized in the hypothalamus and stored in the pituitary until released into the peripheral circulation. Because of the blood/brain barrier, oxytocin secreted from the pituitary cannot reenter the brain. Oxytocin receptors in the body are widespread and include the heart, uterus, testes, and regions of the spinal cord that regulate the autonomic nervous system. (While no oxytocin receptors have as of yet been identified in the mouth, there is currently a research effort at Columbia University to identify oxytocin receptors in the mouth and eyes in the context of using a combination of oxytocin and secretin to treat dry eyes and dry mouth; Welch, 2015). The hypothalamus also releases oxytocin directly in the brain where it acts as a neurotransmitter, coordinating a large number of physiological processes that affect behavior. Thus, oxytocin has endogenous effects on neurotransmission within the brain and exogenous effects systemically as a hormone secreted from the pituitary gland.

Only one oxytocin receptor gene, (OXTR), has been identified; it is a G-protein linked receptor (Gimpl and

Fahrenholz, 2001). There are three known OXTR polymorphisms: G(guanine) G, A(adenine) G, and AA, reflecting the allelic nucleotides present in the gene. These small genetic differences result in differing effects on human behavior. For example, individuals with the GG allele have higher levels of circulating oxytocin. Consequently, these individuals more strongly reflect the prosocial behaviors associated with oxytocin versus those with the AG and AA types (Rodrigues *et al.*, 2009). While genomic information is transmitted to offspring from parental generations, recent evidence indicates that epigenetic mechanisms are capable of mediating this transmission (Kumsta *et al.*, 2013). Epigenetics refers to changes in gene function unrelated to changes in DNA sequence. DNA methylation is one epigenetic mechanism by which cells can control transcription through modifications of the target gene. Greater methylation of the DNA reduces the expression of the gene (Jack *et al.*, 2012). Behavioral neuroscientists now understand epigenetics as a biological mechanism in which environmental influences result in changes in physiology and thus behavior; 'nurture's effect on nature'. Epigenetics has been characterized as the 'new frontier in neuroendocrinology' (McCarthy and Crews, 2008).

Oxytocin is uniquely found in all mammalian species—social animals, living and reproducing in pairs or groups (Carter, 1998). The hormone has had a major role from deep in evolutionary history of promoting mammals to seek a range of mating partners, to prefer specific partners, and to attach to a partner long enough to accomplish parenting duties that permit the survival of offspring (Fisher *et al.*, 2006). Animal studies provide evidence that the quality of maternal behavior early in life has an epigenetic effect on the development of OXTR receptors. In rodent models, the licking/grooming behavior of the dam has been demonstrated to have this epigenetic effect resulting in offspring exhibiting less stress-related behaviors and more sociability (Weaver, 2007). Differential early handling experiences in prairie voles are associated with long-term social attachment behaviors, as well as anxiety-reduced behaviors related to oxytocin (Carter, 2003; Bales *et al.*, 2011). Oxytocin plays a key role in maintaining social relationships in chimpanzees beyond genetic relationships, with cooperative relationships in social grooming facilitated by oxytocin (Crockford *et al.*, 2013). Oxytocin has been demonstrated to have a reliable effect of increasing pain tolerance in 20 of 33 animal studies reviewed (Rash *et al.*, 2014).

Oxytocin and human behavior

Oxytocin is basic to human reproduction (Carter, 1990, 2014). As indicated, oxytocin is associated with the

bonding between mother and child. Cuddling/touching of the child by the mother has a significant impact on oxytocin release (Carter, 1998; Strathearn, 2011). Additionally, in the early stages of infant development, such cuddling is thought to increase the development of OXTR receptors (Fleming *et al*, 2002; Keverne and Curley, 2008). In general, oxytocin acts to permit the high levels of social sensitivity and attunement necessary for human sociality and for maternal caregiving (Francis *et al*, 2002; Carter, 2003).

The evolution and survival of *Homo sapiens* has been facilitated by social intelligence and social communication (Hrdy, 2009). Survival and reproduction depend on adapting social and reproductive behavior to environmental and social demands (Carter, 1998). Humans' large cortex, high levels of social recognition, and complex social interactions could not have evolved without the physiological and behavioral function of oxytocin (Carter, 2014). Oxytocin has the opposite effect on behavior from the 'fight or flight' hormones vasopressin and adrenaline, which increase stress, danger-readiness, and wariness of strangers. Oxytocin reduces anxiety and stress, increases the pain threshold, reduces depression, and enables the body to relax (Uvnäs-Moberg, 2003).

Zak and colleagues published the first study to suggest that oxytocin in humans was related to social behavior, thus consistent with animal studies (Zak *et al*, 2004). Investigators demonstrated that in an exchange of money requiring reciprocity, trusting behavior in the exchange was associated with higher levels of circulating oxytocin.

Individuals with AG/AA alleles of the OXTR gene display higher physiological and dispositional stress reactivity (Rodrigues *et al*, 2009). Impaired oxytocin signaling may be a biomarker of anxiety in humans and a potential target for therapeutic development in individuals with anxiety disorders (Carson *et al*, 2014). Human touch increases circulating oxytocin, thus reducing stress and promoting self-soothing (Champagne and Rissman, 2011; Ellingsen *et al*, 2014; Uvnäs-Moberg *et al*, 2015).

Empathy developed in neuroevolution in the context of parental care in mammals and the neurobiological mechanisms associated with oxytocin that underlie its operation (Carter *et al*, 2009; Decety, 2011). Compared to individuals homozygous for the G allele (GG), AG/AA individuals exhibit lower behavioral and dispositional empathy. (Rodrigues *et al*, 2009) A number of studies have documented the relationship of oxytocin to empathy (Feeser *et al*, 2015; Luo *et al*, 2015; Uzefovsky *et al*, 2015).

Epigenetic regulation of the OXTR receptor gene through methylation appears to play a critical role in social attachment and social cognition, as well as anxiety and stress-related behaviors (Kumsta *et al*, 2013; Ziegler *et al*, 2015). Early abuse of females results in decreased oxytocin levels in comparison with females without such abuse (Heim *et al*, 2009; Champagne and Rissman, 2011). Evidence also suggests the developing oxytocin system is significantly impaired in children reared in institutions associated with severely depriving conditions, compared to children reared in a typical home environment (Wisner Fries *et al*, 2005; Champagne and Rissman, 2011). A retrospective, self-report assessment of maternal care

suggests the transmission of parental bonding style across generations, independent of socioeconomic status, maternal, or daughter temperament (Miller *et al*, 1997; Champagne, 2008; Dias *et al*, 2015). A mother's own attachment to her mother is a good predictor of her infant's attachment to her, most likely the result of the epigenetic impact on OXTR receptors (Fleming *et al*, 2002). Maternal neglect, both physical and emotional, is a pervasive public health challenge with serious long-term effects on child development (Strathearn, 2011).

Research suggests that oxytocin deficits may play a role in psycho-social dysfunctions including autism (Andari *et al*, 2010; Chen and Johnson, 2012), borderline personality disorders (Simeon *et al*, 2011), social anxiety disorder/fear (Guastella *et al*, 2009; Labuschagne *et al*, 2010), and callous-emotional behavior and conduct problems in adolescents (Dadds *et al*, 2014a,b). Adolescent boys with significant conduct problems and exhibiting callous-unemotional traits exhibit high levels of methylation of the OXTR gene lowering circulating oxytocin and resulting in the functional impairment of empathy (Cecil *et al*, 2014). Aspects of psycho-social pathology may be informed by further understanding of the epigenetic process and its functional significance (Dadds *et al*, 2014a,b).

The therapeutic use of intranasally administered oxytocin

Research on the association of oxytocin with multiple prosocial behaviors has led to experimental studies on the effect of administering oxytocin to humans (Guastella *et al*, 2013). Oxytocin does not pass the blood-brain barrier when administered intravenously and is destroyed in the gastrointestinal tract. However, neuropeptides do cross the blood-brain barrier when administered intranasally (Born *et al*, 2002). Intranasal oxytocin has a duration of effect of 2–4 h (Huffmeijer *et al*, 2012). In a seminal study published in *Nature*, Kosfeld and colleagues analyzed the effect of exogenously administered oxytocin on individuals' decision in a trust game with tangible monetary risks at stake (Kosfeld *et al*, 2005). Participants in the study were administered 24 IU oxytocin (Syntocinon Spray, Wirkstoff: Oxytocin; Pharmazeutischer Unternehmer: Rome, Italy) or a placebo 50 min before the start of the trust experiment. The results indicated that oxytocin specifically affected trust in interpersonal interactions.

A critical review of the influence of oxytocin nasal spray in humans concluded that oxytocin nasal spray impressively impacts social and behavioral processes (Guastella and Macleod, 2012). These include reductions in fear and anxiety in social situations, the facilitation of reward cues during social contact, and the enhancement of social salience to enable more effective responses to social information. Intranasal oxytocin has been demonstrated to improve therapy for social anxiety disorder (Guastella *et al*, 2009). Intranasal administration of oxytocin augments endogenous pain inhibitory capacity and reduces negative mood states, including anxiety (Goodin *et al*, 2014). Both animal and human research has found that intranasal oxytocin administration lowered pain perception (Rash *et al*, 2014). Intranasal oxytocin attenuates the fear

response (Acheson *et al*, 2013; Koch *et al*, 2014; Puglia *et al*, 2015). Empathy is increased after intranasal oxytocin administration (Hurlemann *et al*, 2010; Simeon *et al*, 2011). There is a potential therapeutic role for intranasal administration of oxytocin in children on the autism spectrum (Carter, 2007; Jacob *et al*, 2007; Gregory *et al*, 2009; Andari *et al*, 2010; Guastella *et al*, 2012, 2015). Intranasal oxytocin has also been investigated in individuals with borderline personality disorder (Simeon *et al*, 2011). A magnetic resonance imaging experiment found that oxytocin administered intranasally acts to limit the control of the amygdala while simultaneously augmenting the medial prefrontal cortex function to facilitate the extinction of conditioned fear (Eckstein *et al*, 2015).

Research potentials for oral medicine

Oxytocin is receiving increasing attention in behavioral research due to its promotion of social behavior and its regulation of stress, anxiety, fear, and pain tolerance, all factors affecting oral health care. Additionally, it has been demonstrated to modulate emotional empathy, trust, as well as to be responsive to touch. Endogenous oxytocin can be measured non-invasively through urinary levels or salivary samples (Crockford *et al*, 2014). Such a non-invasive assessment can be related to a number of behavioral variables of interest in oral medicine, including the therapeutic use of intranasal oxytocin.

Maternal anxiety has been identified as contributor to the uncooperative behavior of children in the dental environment (Johnson and Baldwin, 1968). As stated previously, the early bonding relationship between mother and child affects the child's behavior through epigenetic effects on the oxytocin system. Studies of mothers' anxiety and oxytocin levels in relationship to their children's anxiety, oxytocin levels, and behavior in receiving dental care could assist in understanding cooperation of children in the dental setting. Mothers with reduced oxytocin receptors and circulating oxytocin would be hypothesized to provide lower levels of empathic bonding with their children and thus would have more anxious children. As previously indicated, epigenetic mechanisms cross generations, with an effect of grandmother to mother to child (Miller *et al*, 1997; Champagne, 2008; Dias *et al*, 2015).

The administration of intranasal oxytocin could have a role in reducing anxiety in adults and improving cooperative behavior in children when receiving dental care. Administration of oxytocin could facilitate the extinction of conditioned fear or enhance empathy and/or trust. A more focused role for the therapeutic use of oxytocin may be a potential in children whose history includes autism or psycho-social problems such as callous-emotional traits or misconduct.

Human touch results in a spike in oxytocin levels resulting in a reduction in stress reactivity (Uvnäs-Moberg *et al*, 2015). Touch could play a role in reducing anxiety in dental care. One study demonstrates a positive relationship between touch and children's cooperative behavior (Greenbaum *et al*, 1993). Research is necessary to understand the relationship of touch to a reduction in anxiety/

stress reactivity and to oxytocin levels when receiving oral health care.

Empathy, both intellectual and emotional, is an important personality characteristic for individuals in the health professions (Nash, 2010). Oxytocin is understood to be the 'empathy hormone', essential to building trust. Because of the power differential existing between dentist and patient, a critical dimension of the professional relationship is the trust the patient has for the dentist. Studies of oxytocin levels in patients relative to the trust they have for their dentist may enlarge understandings of the dentist/patient relationship.

Conclusion

Neuroscience is helping explicate the foundations for many aspects of human behavior. Translating basic neuroscience research on the relationship of the oxytocin system to human behavior offers significant opportunity for behavioral and other research in oral medicine, research with the potential to improve the delivery of oral health care.

Author contributions

The author has conducted all of the research and writing associated with this Letter to the Editor.

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